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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	
First Inventor	FRANCIS SMITH
Title	IMPROVED OPHTHALMIC SOLU
Express Mail Label No.	EF107995208US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☑ Fee Transmittal Form (e.g., PTO/SB/17) *(Submit an original and a duplicate for fee processing)*
2. ☑ Applicant claims small entity status. See 37 CFR 1.27.
3. ☑ Specification [*Total Pages* 20] *(preferred arrangement set forth below)*
   - Descriptive title of the invention
   - Cross Reference to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to sequence listing, a table, or a computer program listing appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
4. ☐ Drawing(s) *(35 U.S.C. 113)* [*Total Sheets* ☐]
5. Oath or Declaration [*Total Pages* ☐]
   a. ☑ Newly executed (original or copy)
   b. ☐ Copy from a prior application (37 CFR 1.63 (d)) *(for continuation/divisional with Box 17 completed)*
      i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. ☐ Application Data Sheet. See 37 CFR 1.76

ADDRESS TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231

7. ☐ CD-ROM or CD-R in duplicate, large table or Computer Program *(Appendix)*
8. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. ☐ Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ paper
   c. ☐ Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

9. ☐ Assignment Papers (cover sheet & document(s))
10. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)* ☐ Power of Attorney
11. ☐ English Translation Document *(if applicable)*
12. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
13. ☐ Preliminary Amendment
14. ☐ Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. ☐ Other: .....

17. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in a preliminary amendment, or in an Application Data Sheet under 37 CFR 1.76:*

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: _____ / _____

Prior application information: Examiner _____ *Group / Art Unit:* _____

For CONTINUATION OR DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

18. CORRESPONDENCE ADDRESS

☐ *Customer Number or Bar Code Label* (Insert Customer No. or Attach bar code label here) or ☐ *Correspondence address below*

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Name (Print/Type)	Chris Blank	Registration No. (Attorney/Agent)	31,237
Signature		Date	11-3-00

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231

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November 4, 2000

Small Entity Declaration and Certificate of Mailing

The following correspondence is being deposited with the United States mail, Express mail addressed to the above address. Applicants named in the attached applications qualify as small entities under the law to the best of my knowledge.

Express Mail No. EF107995208US

Respectfully,

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Improved Ophthalmic and Contact Lens Solutions Comprising Imidazole

Inventors

Frank X. Smith
John Randall Tracey

Summary of the Invention

The present invention relates to contact lens care solutions that have improved ability to resist protein deposition and to provide lenses treated with such solutions to stabilise proteins more effectively, and to decrease the degree of other polymeric depositions on said lenses, such as polymeric preservative deposition of the lenses. The solutions of the present invention employ imidazole as an additive to state of the art solutions in order to decrease the denaturalization of proteins during cleaning cycles and to coat treated lenses to decrease the number of active binding sites on the lenses.

The present invention comprises 0.01 to 5 weight percent of imidazole and a second contact lens solution agent. These agents may include but are not limited to includes an effective amount of a preservative component, for example, an effective preserving amount of a non-oxidative antimicrobial component. Any suitable preservative component may be employed provided that it functions as a preservative and has no significant detrimental effect on the contact lens being treated or the wearer of the treated contact lens. Examples of useful preservative components include, but are not limited to, poly[dimethylimino-2-butene-1,4-diyl] chloride, alpha [4-tris (2-hydroethyl) anunoniumdichloride (available from Onyx Corporation under the trademark Polyquai-ternium 1 Registered TM), benzalkonium halides such as benzalkonium chloride, alexidine salts, chlorhexidine salts, hexamethylene biguanimides and their polymers, and the like and mixtures thereof

The subtilisin enzymes are broken down into two sub-classes, subtilisin A and subtilisin B. In the subtilisin A grouping are enzymes derived from such species are B. subtilis, B. liceniformis and B. pumilis. Organisms in this sub-class produce little or not neutral protease or amylase. The subtilisin B. sub-class is made up of enzymes from such organisms a B. subtilis, B. subtilis var. amylosacchariticus, B. amyloliquefaciens and B. subtilis NRRL B341 1. These organisms product neutral proteases and amylases on a level about comparable to their alkaline protease production. One or more enzymes from the subtilisin A sub-class are particularly useful.

In addition other preferred enzymes are, for example, pancreatin, trypsin, collagenase, keratinase, carboxylase, aminopeptidase, elastase, and aspergillo-peptidase A and B, pronase E (from S. griseus) and dispase (from Bacillus polymyxa).

An effective amount of enzyme is to be used in the practice of this invention. Such amount will be that amount which effects removal in a reasonable time (for example overnight) of substantially all of at least one type of debris from a lens due to normal wear. this standard is stated with reference to contact lens wearers with a history of normal pattern of lens debris accretion, not the very small group who may at one time or another have a significantly increased rate of debris accretion such that cleaning is recommended every day, or every two or three days.

The amount of enzyme required to make an effective cleaner will depend on several factors, including the inherent activity of the enzyme, and the extent of its interaction with the hydrogen peroxide present.

As a basic yardstick, the working solution should contain sufficient enzyme to provide about 0.00 1 to about 3 Anson units of activity, preferably about 0.01 to about 1 Anson units, per single lens treatment. Higher or lower amounts may be used. Enzyme activity is pH dependent so for any given enzyme, there is a particular pH range that is most effective and the solution may be formulated to adjust the pH for optimal enzyme activity.

EXAMPLE
Reduced Protein Deposition

Contact lenses were soaked and heated in test solutions to which a radio-labeled lysozyme was present in a known amount for a period of 12 hours at 37 degrees Celsius. The lenses were rinsed with distilled water in order to remove residual solution. The lenses were then assayed for protein deposition using a Beckman BioGamma 1 counter. Results were reported in ug/lens.

	Lens A ug/lens	Lens B ug/lens	Average ug/lens
Phosphate buffer control	1,043	865	954
1% Imidazole	16	11	14

The imidazole was a 1 percent w/v solution. The matrix control was phosphate buffer and sodium chloride. The imidazole-hydrogen peroxide solution had lower protein binding than the control.

EXAMPLE

Reduced Preservative Binding

Contact lenses were soaked and heated in test solutions to which a radio-labeled C^{14}-PHMB solution in a known concentration for a period of 12 hours at 37 degrees Celsius. The lenses were rinsed with distilled water in order to remove residual solution. The lenses were then assayed for the radio-labeled protein deposition using a Beckman BioGamma 1 counter. Results were reported in ug/lens.

Solution	Lens A ug/lens	Lens B ug/lens	Average ug/lens
1% imidazole in phosphate buffer	21	17	19
Phosphate buffer control	73	64	68.5

The imidazole was at a 1 percent w/v solution in the phosphate buffer. The control was phosphate buffer and sodium chloride. The imidazole solution had a lower cationic preservative adsorption than the control.

EXAMPLE
Inhibition of Protein Deposition

Isotonic aqueous phosphate buffered solutions were prepared and adjusted to pH 7.4. Contact lenses

were soaked in 25 mL of the test solutions overnight. Afterwards, lysozyme was added to the tubes and warmed to 37 degrees Celsius for 12 hours. The lenses were rinsed with distilled water in order to remove residual solution. The lenses were assayed for protein deposition by the BCA method and detected on a HP PDA Spectrophotometer. Results were reported in ug/lens.

Solution	ug lysozyme per lens
Marketed Product Control (phosphate buffer, Poloxamer)	>18.3
Phosphate buffer control	>26.16
1% Imidazole - hydrogen peroxide	3.52

The matrix control was phosphate buffer and sodium chloride. The imidazole solution had lower protein binding than the controls.

EXAMPLE

Protein Stability (Experiment BCL075-126)

Test solutions were prepared according to the formulas indicated in the table had undenatured protein added in a control and were heated to approximately 80 degrees Celsius as indicated. Each sample was observed for clarity. This test provides useful results for indicating the protein is stabilized in comparison with other solutions subjected to the same test regimen.

Weight	10	8	7	6	4	3	2	1	
Solution	80 °C 15 min	80 °C 30 min	80 °C 45 min	80 °C 60 min	Ambient 15 min	Ambient 30 min	Ambient 24 hour	Ambient 48 hour	Total
I	0	0	0	1	2	2	3	3	29
II	1	2	3	3	3	3	3	3	95
III	3	3	3	3	3	3	3	3	123
IV	0	1	3	3	3	3	3	3	77
V	1	3	3	3	3	3	3	3	103
VI	1	3	3	3	3	3	3	3	103

I. 1% imidazole in phosphate buffer
II. phosphate buffer control
III. marketed product having the general composition: A sterile, aqueous, buffered, slightly hypertonic solution containing PEO sorbitan monolaurate and a betaine surfactant as cleaning agents; a slilicone glycol copolymer, a cellulosic viscosifier preserved with chlorhexidine gluconate (0.003%), polyaminopropyl biquanide (0.0005% and edetate disodium (0.05%).
IV. marketed product having the general composition: A sterile, isotonic solution that contains boric acid, edetate disodium, poloxamine, sodium borate and sodium chloride; preserved with DYMED (polyaminopropyl biquanide) 0.00005%.
V. marketed product having the general composition: A sterile, isotonic solution that contains

HYDRANATE (hydroxyalkylphosphonate), boric acid, edetate disodium, poloxamine, sodium borate and sodium chloride; preserved with DYMED (polyaminopropyl biquanide) 0.0001%.

VI. marketed product having the general composition: A sterile isotonic aqueous solution containing sodium chloride, polyoxyethylene polyoxypropylene block copolymer, sodium phosphate dibasic, sodium phosphate monobasic, and preserved with edetate disodium dihydrate 0.025% and polyhexanide 0.0001%.

A weighting factor as indicated in the table was used to multiply each result. 0 indicated a clear sample; 1 slightly turbid, 2 turbid, and 3 indicated cloudy and separate phases (precipitate). The data illustrates the ability of imidazole to stabilize the protein and thus decrease the extent of opacification on the contact lens from the protein deposit. The formula performed superior to the marketed products.

What is claimed is:

1. A lens care solution comprising:

0.01 to about *5* weight percent of imidazole;

an effective amount of biologically compatible buffer system to maintain the pH of the solution between *6.5* and 7.8 pH, and

the balance water.

2. A lens care solution comprising:

0.0 ito about *5* weight percent of imidazole; an effective amount of tonicity agent ; and

the balance water

3 A lens care solution comprising:

0.0 ito about 5 weight percent of imidazole; an effective amount of a preservative agent;

and the balance water

3. A method for treating a contact lens in order to decrease its affinity to protein

deposition which comprises the step of:
Soaking a contact lens in an aqueous solution comprising 0.01 to 5 weight percent imidazole.

4. The solution of claim 1 which further comprises 0.01 to 2 weight percent of a physiologically acceptable tonicity agent adjusted so the solution is isotonic between 200 and 400 mOsm

5. The solution of claim 4 that further comprises 0.00001 to 0.1 weight percent of a preservative.

6. The solution of claim 1 wherein the buffer is selected from the group consisting of organic amines, organic carboxylic acids, amphoterics, phosphates, or borates.

7. The method of claim 3 wherein the aqueous solution further comprises the buffer bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane (Bis–Tris) and its salts.

8. The method of claim 3 wherein the aqueous solution further comprises the 1,2-bis[tris(hydroxymethyl)-methylamino}propane (Bis-Tris Propane) and its salts.

9. The method of claim 3 wherein the aqueous solution further comprises the N-tris(hydroxymethyl) methyl glycine (Tricine) and its salts.

10. The method of claim 3 wherein the aqueous solution further comprises the N,N-bis(2-hydroxyethyl)-glycine (Bicine) and its salts.

11. The method of claim 3 wherein the aqueous solution further comprises the betaine and its salts.

12. The method of claim 3 wherein the aqueous solution further comprises the buffer phosphate and its salts

13. The method of claim 3 wherein the aqueous solution further comprises the buffer is borate and its salts

14. The method of claim 3 wherein the aqueous solution further comprises the is citrate and its salts

15. The method of claim 3 wherein the aqueous solution further comprises is TRIS and its

salts

16. The method of claim 3 wherein the aqueous solution further comprises the buffer is 2-amino-2-methyl-1,3-propanediol and its salts

17. The method of claim 3 wherein the aqueous solution further comprises the buffer is triisopropanolamine and its salts

18. The method of claim 3 wherein the aqueous solution further comprises the buffer is carnitine and its salts

19. The method of claim 3 wherein the aqueous solution further comprises the buffer is dimethyl glutamate and its salts

20. The method of claim 3 wherein the aqueous solution further comprises the buffer is creatine and its salts

21. The method of claim 3 wherein the aqueous solution further comprises the buffer is diethanolamine and its salts

22. The method of claim 3 wherein the aqueous solution further comprises the buffer is diisopropylamine and its salts

23. The method of claim 3 wherein the aqueous solution further comprises the buffer is triethanolamine and its salts

24. The method of claim 3 wherein the aqueous solution further comprises the buffer is triethylamine and its salts

25. The method of claim 3 wherein the aqueous solution further comprises the buffer is dimethyl aspartic acid and its salts

26. The method of claim 3 wherein the aqueous solution further comprises the buffer is imidazole and its salts

27. The method of claim 3 wherein the aqueous solution further comprises the buffer is histidine and its salts

28. The method of claim 3 wherein the aqueous solution further comprises the buffer is methyl aspartate and its salts.

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing **OR** ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	
First Named Inventor	FRANCIS X. SMITH
COMPLETE IF KNOWN	
Application Number	/
Filing Date	
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Ophthalmic and Contact lens Solution Comprising Imidazole

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☐ was filed on (MM/DD/YYYY) ☐ as United States Application Number or PCT International Application Number ☐ (if applicable).

and was amended on (MM/DD/YYYY) ☐

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)
60/163453	11-04-99

☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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DECLARATION — Utility or Design Patent Application

Direct all correspondence to: ☐ Customer Number or Bar Code Label [ ] OR ☐ Correspondence address below

Name: Chris Blank

Address: 4 Bicentennial Square

Address: Suite 2B

City: Concord | State: NH | ZIP: 03301

Country: USA | Telephone: 603 227 5248 | Fax: 603 227 5263

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR : ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]): Francis X. | Family Name or Surname: Smith

Inventor's Signature: Francis X Smith | Date: 11-03-00

Residence: City: Salem | State: NH | Country: USA | Citizenship: USA

Mailing Address: 22 Fox Run

Mailing Address:

City: Salem | State: NH | ZIP: | Country: USA

NAME OF SECOND INVENTOR: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]): | Family Name or Surname:

Inventor's Signature: | Date:

Residence: City: | State: | Country: | Citizenship:

Mailing Address:

Mailing Address:

City: | State: | ZIP: | Country:

☐ Additional inventors are being named on the ____supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.